PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or Agent's file reference 25224 WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/08229	International filing date *(day/month/year)* 07.25.2003	Priority date *(day/month/year)* 07.26.2002
International Patent Classification (IPC) or national classification and IPC A61K38/18		
Applicant BAHLMANN, Ferdinand Hermann et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets including this title page.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Instruction 607 of Administrative Instructions of the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement according to Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand 02.26.2004	Date of completion of this report 11.17.2004
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I. Basis of the report

1. This report has been drawn up on the basis of the following elements *(the replacement sheets received by the receiving office in response to an invitation according to Article 14 are considered in the present report as "originally filed" and are not annexed to the report as they contain no amendments (Rules 70.16 and 70.17).):*

Description, pages:
1-27, 29-59 as originally filed

28 received on 10.18.2004 by fax

Claims, No.:

Insert no. here as originally filed

1-43 received on 10.18.2004 by fax

Drawings, sheets:

1/15-15/15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been written disregarding (some of) the amendments, which were considered as going beyond the description of the invention, as filed, as is indicated below (Rule 70.2(c)):

(All replacement sheets comprising amendments of this nature should be indicated in point 1 and attached to this report).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non- obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 24-32,38-43 (Industrial Applicability)

because:

☒ the said international application, or the said claims Nos. 24-32,28-43 (Industrial Applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict the claims or pay additional fees.

3. This Authority found that, according to Rules 13.1, 13.2 and 13.3:

   ☐ the requirement of unity of invention is complied with.

   ☐ the requirement of unity of invention is not complied with, for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23,29-32,43
	No:	Claims	24-28,33-42
Inventive Step (IS)	Yes:	Claims	1-3
	No:	Claims	4-23,29-32,43
Industrial Applicability (IA)	Yes:	Claims	1-23,33-37
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

1. Claims 24-32 and 38-43 relate to a subject-matter which, in the opinion of this authority, falls under Rule 67.1 (iv) PCT. No opinion is therefore given on the industrial applicability of the subject-matter of these claims (Article 34(4) a) (i) PCT).

Re Item IV

2. This authority has found that the international application comprises a plurality of inventions or groups of inventions which are not linked so as to form a single general inventive concept (Rule 13.1 PCT), namely:

1. Claims 1-14, 24-28, 29-32 (in part), 33-43: Use of EPO in a dose of from 500 to 2 000 units/week/patient to stimulate endothelial progenitor cells, for the therapy of diseases and corresponding pharmaceutical compositions.

2. Claims 15-23, 29-32 (in part): Use of EPO for producing transplantable endothelial cell preparations, for producing cell-containing organ or tissue systems and for producing heart valves.

The reasons for this are as follows: based on the claims and the description, the problem underlying the present invention is to provide compositions and methods for improved stimulation of endothelial progenitor cells and for the therapy of disorders associated therewith, and endothelial cell preparations. The proposed solution is the administration of EPO on the one hand in general and on the other hand in a dose of from 500 to 2 000 units of EPO/week/patient. Unity is therefore lacking a priori. Apart from this, the documents WO 98 10650 A, US 5 980 887 A, BUEMI M et al. (J. Nephrol.) and KRAUSE K et al. (European Heart Journal) describe mitogenic and migratory effects of EPO on endothelial cells and its angiogenic effect. Since the use of EPO to stimulate endothelial cells including the formation of new blood vessels is known, inventions 1 and 2 are not linked by a common inventive concept. The requirement of unity of the invention (Rule 13.1 PCT) is thus not fulfilled since there is no technical relationship between the subject-matters of the groups of inventions involving one or more of the same or corresponding special technical features as required by

Rule 13.2 PCT.

Re Item V

3. Reference is made to the following documents of the international search report and the passages cited therein:

D1: WO 03/057242 A

D2: WO 02/14356 A

D3: US 2002/065214 A1

D4: WO 00/61164 A

D5: WO 98/10650 A

D6: US-A-5 980 887

D7: NEPHROLOGY DIALYSIS TRANSPLANTATION, Vol. 12(9), 1997, page A190

D8: JOURNAL OF NEPHROLOGY 2002 ITALY, Vol. 15, No. 2, 2002, pages 97-103

D9: INTERNATIONAL JOURNAL OF HEMATOLOGY, Vol. 70, No. 1, pages 1-6

D10: EUROPEAN HEART JOURNAL, Vol. 22, No. Abstract Supplement, September 2001 (2001-09), page 154

D11: NEPHROLOGY DIALYSIS TRANSPLANTATION, Vol. 10(2), pages 74-79

D12: DATABASE BIOSIS [Online]; 2002, KASHIWAGI M ET AL.: "Hypertension in a pregnancy with renal anemia after recombinant human erythropoietin (rhEPO) therapy."

D13: DATABASE BIOSIS [Online]; 1997, CONRAD KIRK P ET AL.: "Placental cytokines and the pathogenesis of preeclampsia"

D14: WO 03/037273 A

D15: DATABASE EMBASE [Online]; 2000, CASES A: "Recombinant human erythropoietin treatment in chronic renal failure: Effects on hemostasis and vasculature"

D16: DATABASE MEDLINE [online]; 1996, BRAGA J ET AL.: "Maternal and perinatal implications of the use of human recombinant erythropoietin."

D17: WO 02/085940 A

D18: DATABASE BIOSIS [Online]; 2001, ARCASOY MURAT O ET AL.: "Erythropoietin (EPO) stimulates angiogenesis in vivo and promotes wound healing"

D19: WO 89/07944 A

D20: WO 92/15323 A
D21: US-A-4 992 419
D22: US-A-5 198 417
D23: DATABASE BIOSIS [Online]; 1998, ALVAREZ ARROYO MARIA VICTORIA ET AL.: "Role of vascular endothelial growth factor on erythropoietin-related endothelial cell proliferation"

3.1 Document D1 discloses the use of EPO for treating heart failure. Assuming that the priority is valid, document D1 is not included in the prior art for the international preliminary examination.

3.2 Document D2 describes the use of EPO for treating chronic heart failure where appropriate associated with renal failure with 5, 75, 150 and 200 IU/kg, once to three times per week (claims 35 and 36).

3.3 Document D3 discloses the use of EPO in combination with an iron compound for improving cardiac function. A dose of 500-10 000 IU/week is administered.

3.4 Document D4 discloses pharmaceutical compositions comprising EPO for protection against hypotension, ischemia, myocardial infarction and inflammation.

3.5 Document D5 describes the protection of endothelial cells from damage by certain does of EPO, and the demonstration that EPO has a mitogenic and migratory effect on endothelial cells, which represents a key step in angiogenesis. Damage to be treated according to the invention includes that caused by inflammation, cardiac diseases and atherosclerosis. EPO is used for the treatment of anemia (associated with chronic renal failure).

3.6 Document D6 describes a method for the treatment of damaged blood vessels, where EPO is administered as endothelial cell mitogen, and endothelial progenitor cells are isolated and readministered. This method can also be used to treat a wide variety of ischemias (e.g. renal).

3.7 Document D7 describes the protective effect of EPO against atherosclerosis in hypercholesterolemic rabbits.

3.8 Document D8 describes the role of rEPO in chronic inflammatory diseases (neopterin reduction) and the stimulation of endothelial cells (angiogenesis) apart from the conventional treatment of anemia (in patients with chronic renal failure). There are references to the suitability of EPO for wound healing. The synergy of VEGF and EPO is described.

3.9 Document D9 discloses the angiogenic activity of EPO and the stimulation of proliferation and migration of endothelial cells.

3.10 Document D10 discloses the angiogenic potential of EPO.

3.11 Document D11 describes the association between EPO treatment and high blood pressure.

3.12 Document D12 discloses that EPO treatment increases the blood pressure in pregnant women.

3.13 Document D13 is a hypothesis linking preeclampsia with placental cytokines.

3.14 Document D14 discloses the use of EPO for treating acute ischemic renal failure using subpolycythemic doses. The treatment leads to cell repair (example 6). Assuming the priority is valid, document D14 is not included in the prior art for the international preliminary examination.

3.15 Documents D15 and D16 disclose the use of EPO for treating renal failure.

3.16 Document D17 discloses EPO derivatives for treating various diseases such as wound healing, renal failure, cardiovascular disorders and rejection reactions.

3.17 Document D18 discloses the pro-angiogenic effect of EPO and its promotion of wound healing.

3.18 Document D19 discloses neovascularization implants which may be coated with cells able to produce EPO.

3.19 Document D20 discloses a method for increasing the cell population by ex vivo stimulation with a morphogen. EPO is a corresponding factor of the hemopoietic system.

3.20 Document D21 discloses pharmaceutical compositions comprising EPO and L-arginine.

3.21 Document D22 discloses the coadministration of EPO and GM-CSF.

3.22 Document D23 discloses the synergistic interaction of EPO with VEGF.

4. Novelty:

4.1 Claims 1-14 relate to the use of erythropoietin for producing a pharmaceutical composition comprising a dose of from 500 to 2 000 units of EPO/week/patient for treating various diseases. Since none of the documents discloses the use of such doses for treating the stated diseases, the subject-matter of claims 1-14 and of the further dependent claims 29-32 and of claim 43 appears to be novel.

4.2 Claims 15-23 relate to the use of EPO for producing transplantable endothelial cell preparations, for producing cell-containing organ or tissue systems and for producing heart valves. Since none of documents D2-D23 discloses such

methods, the subject-matter of these claims appears to be novel.

4.3 Claims 24 and 38 relate to the use of erythropoietin in a dose of from 500 to 2 000 units of EPO/week/patient to stimulate endothelial cells and to stimulate vasculogenesis, respectively. However, since cardiac diseases and ischemias fall under this definition (e.g. D5 or D6, original claims), the subject-matter of this claim and of claims 25-28 and 38-42 appears not to be novel in relation to (at least) D2 and D3.

4.4 Claims 33 and 34 relate to a pharmaceutical composition comprising erythropoietin in a dose of from 500 to 2 000 units of EPO/week/patient respectively alone and in combination with further active ingredients. Claim 34 appears not to be novel in relation to D2 and D3. Since it is unclear whether the claims relate to single doses or not, the subject-matter of claims 33-37 appears not to be novel in relation to D21-23 either.

5. Inventive step:

5.1 Claims 1 and 2 relate to the use of erythropoietin for producing a pharmaceutical composition comprising a dose of from 500 to 2 000 units of EPO/week/patient for treating chronic and acute renal failure, respectively. Document D2 can be regarded as the closest prior art and discloses the use of EPO for treating renal anemias based on chronic renal failure.
It was shown in the application that, on treatment of chronic or acute renal failure with the subpolycythemic doses according to the invention, a renal tissue regeneration takes place. Since the treatment is carried out in the prior art by compensating the EPO missing from the body with an increase in the hematocrit values, the use of subpolycythemic doses appears not to be obvious.

5.2 Claim 3 relates to the use of erythropoietin for producing a pharmaceutical composition comprising a does of from 500 to 2 000 units of EPO/week/patient for wound healing. Document D18, which is regarded as the closest prior art, discloses the angiogenic function of EPO in wound healing and differs through the dose used.
The problem to be solved is the provision of an improved treatment of wounds. Since such an effect was shown, the subject-matter of claim 3 appears to be

inventive.

5.3 Claim 4 relates to the use of erythropoietin for producing a pharmaceutical composition comprising a does of from 500 to 2 000 units of EPO/week/patient for treating various diseases.
Starting from documents D5-D7 and D11-D13, which disclose the treatment of these diseases with EPO, the problem to be solved is the provision of an improved treatment. Since there is no evidence of an improvement, the subject-matter of claims 4-14, 29-32 and 43 appears not to be inventive.

5.4 The subject-matter of claims 15-23, which is not supported by any data in the application, appears to be an arbitrary application of the properties of EPO which are disclosed in documents D5, D6, D8-D10 and D19-D20 and thus appears not to be inventive.

It is particularly preferred according to the invention for erythropoietin, in all the uses, methods and compositions of the present disclosure, to be used in very small amounts which are below the amounts known to be employed, administering in particular in vivo, i.e. per patient, EPO doses of from 200 to 2 000 units (IU; international units)/week, preferably doses of from 500 to 2 000 IU/week, depending on the severity of the disorder and depending on renal function. The doses, provided according to the invention, of from 200 to 2 000 units (IU)/week and per patient, especially from 500 to 2 000 IU/week and per patient, are subpolycythemic doses, that is doses which do not lead to erythrocytosis with hematocrit values of more than 50%. The subpolycythemic doses provided according to the invention correspond to weekly doses of about 1 to 90 units (IU) of EPO/kg of body weight, in particular 1 to 45 IU of EPO/kg of body weight, or a comparable weekly dose of Aranesp of from 0.005 to 0.45 µg/kg of body weight, in particular 0.005 to 0.225 µg/kg of body weight. Aranesp is a doubly PEGylated EPO. The dose of from 200 to 2 000 units/week per patient, in particular from 500 to 2 000 IU/week and per patient, which is provided according to the invention for the treatment of diseases or pathological states associated with a dysfunction of endothelial progenitor cells is very low compared with the initial dose of 50-150 IU/kg of body weight/week (usually starting with 4 000-8 000 IU/week, but also considerably

higher if the result of therapy is unsatisfactory) normally employed for the therapy of renal anemia.

A particularly preferred embodiment of the invention relates to the use of erythropoietin and/or its derivative as active ingredient for producing a pharmaceutical composition or a medicament for the therapy of pathological states or diseases associated with a dysfunction of endothelial progenitor cells.

An "active ingredient" means according to the invention an endogenous or exogenous substance which on contact with target molecules or target cells or target tissues influences in a differentiated manner specific functions of tissues, organs or organisms. The invention thus provides for erythropoietin as active ingredient of the pharmaceutical composition of the invention influencing the proliferation, differentiation and/or migration behavior of endothelial progenitor cells on contact therewith in a human or animal organism in such a way that dysfunctions of endothelial progenitor cells can be compensated and the diseases occurring as a consequence of these dysfunctions effectively controlled, alleviated or eliminated, or these diseases effectively prevented.

In connection with the present invention, a "pharmaceutical composition" or a "medicament" means a mixture which is used for diagnostic, therapeutic and/or prophylactic purposes, that is promoting or restoring the health of a human

Claims

1. The use of erythropoietin for producing a pharmaceutical composition comprising a dose of from 500 to 2 000 units of EPO/week/patient for the treatment of chronic renal failure.

2. The use of erythropoietin for producing a pharmaceutical composition comprising a dose of from 500 to 2 000 units of EPO/week/patient for the treatment of acute renal failure.

3. The use of erythropoietin for producing a pharmaceutical composition comprising a dose of from 500 to 2 000 units of EPO/week/patient for wound healing.

4. The use of erythropoietin for producing a pharmaceutical composition comprising a dose of from 500 to 2 000 units of EPO/week/patient for the therapy of hypercholesterolemia, diabetes mellitus, endothelium-mediated chronic inflammatory disorders, endotheliosis including reticuloendotheliosis, atherosclerosis, ischemic disorders of the extremities, preeclampsia, Raynaud's disease or pregnancy-induced hypertension.

5. The use as claimed in any of claims 1 to 4, where the pharmaceutical composition is suitable for parenteral, in particular intravenous, intramuscular, intracutaneous or subcutaneous, administration.

6. The use as claimed in claim 5, where the pharmaceutical composition is in the form of an injection or

infusion.

7. The use as claimed in any of claims 1 to 4, where the pharmaceutical composition is suitable for pulmonary administration.

8. The use as claimed in claim 7, where the pharmaceutical composition is in the form of an aqueous solution, nonaqueous solution or powder.

9. The use as claimed in claim 7 or 8, where the pharmaceutical composition is in the form of an aerosol product.

10. The use as claimed in any of claims 1 to 4, where the pharmaceutical composition is suitable for oral administration.

11. The use as claimed in claim 10, where the pharmaceutical composition is in the form of a solution, suspension, emulsion or tablet.

12. The use as claimed in any of claims 1 to 11, where the pharmaceutical composition comprises at least one further active ingredient to stimulate endothelial progenitor cells.

13. The use as claimed in claim 12, where the further active ingredient is VEGF, PIGF, GM-CSF, an HMG-CoA reductase inhibitor and/or an NO donor, especially L-arginine.

14. The use as claimed in claim 13, where the HMG-CoA reductase inhibitor is a statin such as simvastatin, mevastatin or atorvastatin.

15. The use of erythropoietin for producing a transplantable endothelial cell preparation.

16. The use as claimed in claim 15, where endothelial cells are produced in vitro by cultivating endothelial progenitor cells in the presence of erythropoietin.

17. The use as claimed in claim 15 or 16, where the cultivation of the endothelial progenitor cells takes place in the presence of at least one further active ingredient selected from the group consisting of VEGF, PIGF, GM-CSF, an HMG-CoA reductase inhibitor, especially simvastatin, mevastatin or atorvastatin, and an NO donor, especially L-arginine.

18. The use of erythropoietin for the pretreatment and/or further treatment of tissue or organ transplants.

19. The use as claimed in claim 18, where the pretreatment of the tissue or organ transplants takes place with use of isolated endothelial progenitor cells.

20. The use of erythropoietin for producing implantable or transplantable cell-containing in vitro organ or tissue systems, where the in vitro organ or tissue systems are treated with erythropoietin before the transplantation or implantation to induce vasculogenesis and/or endothelial cell formation.

21. The use as claimed in claim 20, where the in vitro organ or tissue systems comprise endothelial progenitor cells.

22. The use of erythropoietin to produce vascular prostheses or heart valves, where the vascular prostheses or heart valves are coated with erythropoietin.

23. The use as claimed in claim 22, where the coating of the vascular prostheses or heart valves comprises endothelial progenitor cells.

24. The use of erythropoietin and/or derivatives thereof in a dose of from 500 to 2 000 units of EPO/week/patient to stimulate physiological mobilization of endothelial progenitor cells, proliferation of endothelial progenitor cells, differentiation of endothelial progenitor cells to endothelial cells and/or migration of endothelial progenitor cells in the direction of an angiogenic or vasculogenic stimulus.

25. The use as claimed in claim 24, where the adhesion ability of differentiating endothelial progenitor cells is increased.

26. The use as claimed in claim 24 or 25, where the stimulation of endothelial progenitor cells leads to the formation of endothelial tissue.

27. The use as claimed in any of claims 24 to 26, where the stimulation of endothelial progenitor cells leads to the formation of new blood vessels.

28. The use of erythropoietin for producing a pharmaceutical composition comprising a dose of from 500 to 2 000 units of EPO/week/patient to stimulate the formation of

endothelial tissue.

29. The use as claimed in any of claims 1 to 28, where erythropoietin is human or animal erythropoietin.

30. The use as claimed in claim 29, where erythropoietin is a derivative, an analog, a modification or a mutein of erythropoietin.

31. The use as claimed in claim 29 or 30, where erythropoietin is isolated from human urine, the urine or plasma of patients suffering from aplastic anemia, tissue cultures of human renal cancer cells, human lymphoblast cells having the ability to produce human erythropoietin, or a hybridoma culture obtained by cell fusion of a human cell line.

32. The use as claimed in claim 29 or 30, where erythropoietin is an erythropoietin produced by DNA recombination techniques.

33. A pharmaceutical composition to stimulate endothelial progenitor cells, to stimulate the formation of endothelial tissue, to stimulate vasculogenesis and/or for the treatment of diseases or pathological states associated with a dysfunction of endothelial progenitor cells, comprising erythropoietin and/or a derivative, an analog, a modification or a mutein thereof as active ingredient in a dose of from 500 to 2000 units of EPO/week/patient, and at least one further active ingredient selected from the group consisting of VEGF, PIGF, GM-CSF, an HMG-CoA reductase inhibitor and an NO donor.

AMENDED PAGE

34. A pharmaceutical composition for the prophylaxis and/or therapy of hypercholesterolemia, diabetes mellitus, endothelium-mediated chronic inflammatory disorders, endotheliosis including reticuloendotheliosis, atherosclerosis, ischemic disorders of the extremities, preeclampsia, Raynaud's disease, pregnancy-induced hypertension, chronic or acute renal failure, especially terminal renal failure, wound healing and sequelae thereof, comprising erythropoietin and/or a derivative, an analog, a modification or a mutein thereof as active ingredient in a dose of from 500 to 2 000 units/week/patient.

35. The pharmaceutical composition as claimed in claim 34, additionally comprising a further active ingredient selected from the group consisting of VEGF, PIGF, GM-CSF, an HMG-CoA reductase inhibitor and an NO donor.

36. The pharmaceutical composition as claimed in claim 33 or 35, where the HMG-CoA reductase inhibitor is a statin such as simvastatin, mevastatin or atorvastatin.

37. The pharmaceutical composition as claimed in claim 33 or 35, where the NO donor is L-arginine.

38. The use of erythropoietin and/or derivatives thereof in a dose of from 500 to 2 000 units of EPO/week/patient for stimulating vasculogenesis.

39. The use of erythropoietin in a dose of from 500 to 2 000 units of EPO/week/patient for the therapy of pathological states or diseases of the human or animal body

associated with a dysfunction of endothelial progenitor cells.

40. The use as claimed in claim 39, where the dysfunction of endothelial progenitor cells consists of their impaired ability to proliferate, their impaired ability to differentiate to endothelial cells, their impaired ability to adhere and/or their impaired ability to migrate in the direction of a vasculogenic or angiogenic stimulus.

41. The use as claimed in claim 39 or 40, where the dysfunction of endothelial progenitor cells impairs or prevents the formation of endothelial tissue and/or blood vessels.

42. The use as claimed in any of claims 39 to 41, where the dysfunction of endothelial progenitor cells has a pathogenic cause.

43. The use as claimed in any of claims 39 to 42, where the pathological states or diseases associated with a dysfunction of endothelial progenitor cells are hypercholesterolemia, diabetes mellitus, endothelium-mediated chronic inflammatory disorders, endotheliosis including reticuloendotheliosis, atherosclerosis, ischemic disorders of the extremities, preeclampsia, Raynaud's disease, pregnancy-induced hypertension, chronic or acute renal failure, especially terminal renal failure, wound healing and sequelae thereof.